Supplemental Information
FDA Pre–Submission Meeting

COSMIIC System – HIVE Recording Module

May 18, 2023

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University of Michigan

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Table 1. Pre-Sub Meeting Request Summary

Proposed Device Name:	HIVE Recording Module
Device Description:	The HIVE recording module records electromyography signals from muscles (intact and reinnervated) residing in people with upper-extremity amputations. These signals are wirelessly transmitted to an external device that interprets the signals to control a terminal device.
Proposed Indication:	The intended use of the device is to provide intuitive functional control of a prosthetic hand.
Type of Meeting:	Pre-IDE Meeting
Purpose of Meeting:	To verify the pre-clinical testing and risk analysis for a wearable version of the device that may be added as an amendment to an existing investigational device exception (IDE) study [redacted].
Specific Meeting Objectives:	Determine if the supplied risk analysis is sufficient – 20 minutes Determine if any additional electronics testing needs to be completed to sufficiently address the risks – 30 minutes
Sponsor Meeting Attendees:	Paul Cederna, MD Cynthia Chestek, PhD Alex Vaskov, PhD Mona Bruch Moore, RAC
Requested Agency Attendees:	*T.B.D.* by FDA-CDRH
Information Package Availability:	The Pre-Sub Meeting Briefing Packet is included in this submission
Suggested Meeting Dates: **Unavailable Dates:**	Monday 7/24/2023 1pm-2pm, 2pm-3pm Friday 7/28/2023 11am-12pm, 1pm-2pm Monday 7/31/2023 1pm-2pm, 2pm-3pm Tuesday 8/1/2023 2pm-3pm, 3pm-4pm
Suggested Meeting Format:	Teleconference

C. DEVICE DESCRIPTION

This presubmission inquiry is being submitted to obtain early feedback on a device being developed through the NIH SPARC HORNET Program (1-U41NS129436-01). This project will develop a fully implantable system, referred to as COSMIIC, that is intended to enable first in human, early feasibility studies for a wide range of medical applications. COSMIIC is based on the modular architecture of the Networked Neuroprosthesis (NNP) designed at Case Western Reserve University. This means different combinations of devices can be networked together for different applications. Here we are requesting feedback on the device specific to our first intended human use of the COSMIIC system: a novel neural sensing module referred to as the HIVE (High density Interconnects with Variable Electronics) recording module.

Our first intended use of the HIVE recording module described below is to provide intuitive functional control of multi-articulated prosthetic hands for upper-limb amputation patients who have received the regenerative peripheral nerve interface (RPNI) surgical procedure. [redacted] Briefly, the RPNI surgical procedure places individual small muscle grafts on the ends of nerve fascicles in the residual limb. The nerve fascicles reinnervate their respective muscle grafts, forming healthy, stable, and long-lasting neuromuscular connections. Under the current IDE study, percutaneous intramuscular bipolar electrodes are being used to test the safety and efficacy of recording directly from RPNIs.

Prior to the completion of the fully implantable HIVE module, we will first test a wearable version of the system using our current percutaneous electrodes. The wearable system is composed of five elements: (1) wearable HIVE recording module, (2) wearable NNP power module (3) percutaneous [redacted] electrodes, (4) smart link controller + socket, and (5) prosthetic hand (Fig. 1). The HIVE recording module will transmit processed signals to the wearable power supply module, which will wirelessly stream packets to the smartlink controller + socket. The EMG signals are then interpreted into movement commands for a terminal device (e.g. a myoelectric prosthetic hand). The following sections will describe each element in detail.

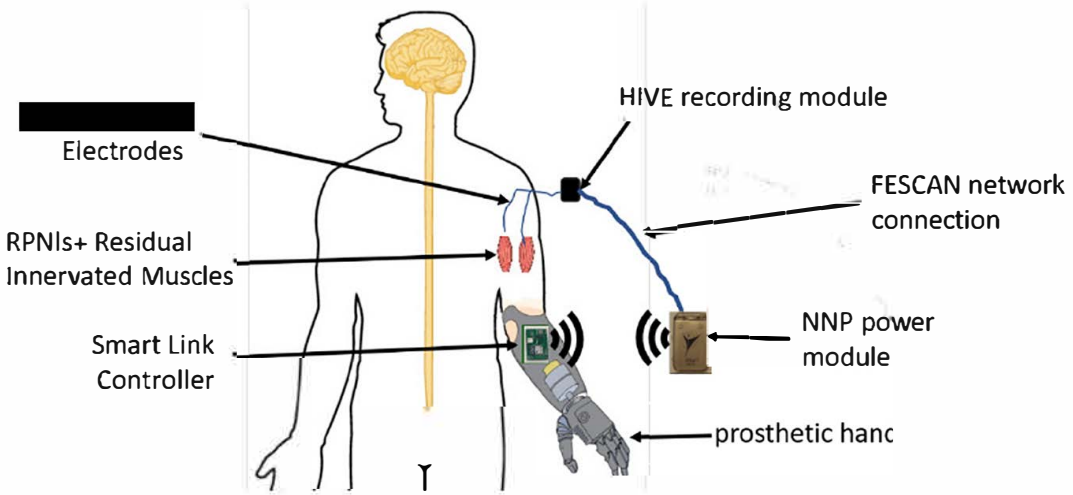

Figure 1: Illustration of the HIVE wearable system. The wearable HIVE recording module sends electromyography (EMG) signals to a wearable NNP power module which wirelessly streams them to a socket mounted prosthetic controller.

Wearable HIVE Recording Module

The wearable HIVE recording module can record electrophysiological signals on up to 64 monopolar electrode contracts and communicate with other modules using the NNP's (Functional Electrical Stimulation Controller Area Network) FESCAN protocol (described in more detail below). The wearable system proposed here does not contain any stimulation modules. The HIVE recording module will contain a two-panel rigid-flex printed circuit board (PCB) where one panel houses a 64-channel feedthrough array connected to an Intan RHD2164 amplifier chip. A STM32L433RI6 (STMicroelectronics) microcontroller unit (MCU) is responsible for programming filtering and sampling settings on the Intan, signal processing, and network communications (Fig. 2). To process EMG, the Intan amplifier will be programmed with the following settings: sample data at 1KSps and apply a 100-500Hz bandpass filter, derived from previous work[1]. The second panel contains the power management and FESCAN circuitry to receive power and communicate with other NNP modules. This design isolates analog and digital signals to separate panels. Intan amplifiers have low power consumption and have previously been used in surgically invasive clinical research[2–5]. No adverse events were noted in these acute studies. We have also previously designed and tested a similar 96 channel circuit board using Intan amplifiers that was optimized to consume <40mW and tested in a surgically invasive application with non-human primates[6]. The primary component changes between the previous board and the HIVE recording module are the more compact 64 channel amplifier and MCU, with other components being substituted due to obsolescence.

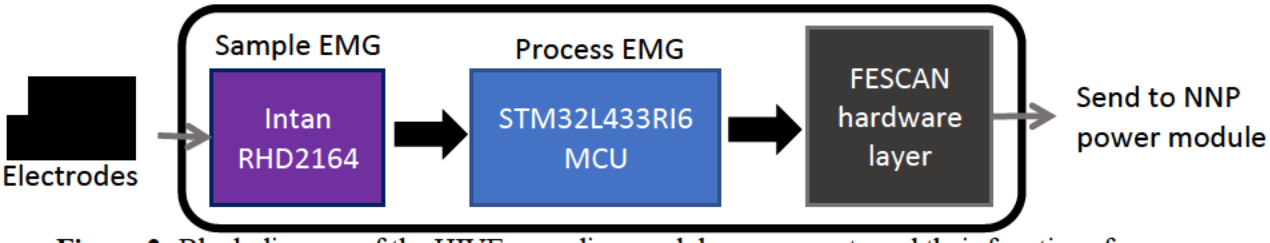

Figure 2: Block diagram of the HIVE recording module components and their functions for processing EMG from the percutaneous [redacted] electrodes.

The HIVE recording PCB will be manufactured by Excello, assembled by Screaming Circuits, and tested at the University of Michigan. The materials used in the sensing unit are typical for modern printed circuit board assemblies (PCBAs). The circuit board is a flat laminated composite with internal copper circuitry and a rigid-flex geometry. The components mounted on the circuit board are general use integrated circuits (ICs) being used as intended by the manufacturer. The below list details specifics of the manufacturing and test plan for each board prior to use:

1. PCB printing (Excello)
    - Institute for Printed Circuits (IPC) class 3 inspection
    - Flying probe test to check for short/open circuits
2. PCB assembly (Screaming Circuits)
    - IPC class 3 inspection
    - Assembly with lead free solder
3. Final testing and assembly (University of Michigan)
    - Power and ground impedance checks
    - Program MCU
    - Functional test to verify recording on all channels and FESCAN communication
    - Mount into plastic enclosure

The HIVE recording module will fit into a 3x3cm plastic enclosure and contain the following connections for this use case: 1) NNP network connection to an external power module, 2) touchproof reference electrode, 3) Adapter to [redacted] electrode connectors.

Risks associated with the HIVE recording module:

1) Damage due to electrostatic discharge

The HIVE recording module will be handled during benchtop testing and when being connected to the participants' percutaneous electrode leads. During handling, high electrostatic discharge (ESD) voltages can permanently damage electrical components inside of the recording module, which could render the device non-functional.

Mitigation: The Intan RHD2164 amplifier contains internal electrostatic discharge diodes that protect against mild ESD events. The HIVE recording module will only be handled by trained study personnel who will ground themselves before handling.

Resolution: If it is determined that the recording module is non-functional immediately after connection despite being functional prior to connection, it will be assumed that the recording module underwent damaging electrostatic discharge. A new tested recording module can be connected to the NNP and percutaneous electrodes.

2) Electrical harm to patient

The recording module may increase the risk of electrical shock to the patient due to leakage current through the [redacted] electrodes.

Mitigation: The Intan pins that are connected to the [redacted] electrodes do not generate current because they are connected to amplifier inputs. To verify this, the recording module will be leakage current tested. To accommodate for future use cases, the device will comply with the ISO 14708-1 standard for active implantable devices.

Resolution: In the wearable system, the [redacted] electrodes and touchproof reference can be quickly disconnected to remove the device from the patient and an adverse event will be logged. The device will be removed from the study and replaced with a new tested recording module.

NNP FESCAN and Power Module

The Networked Neuroprosthesis (NNP), which forms the basis of the COSMIIC library, is already in use in people with spinal cord injuries and provides a range of recording and stimulation capabilities[7]. The NNP provides a starting point for circuitry that has been carefully designed to ensure safety and has previously been approved by FDA [redacted] for use in early clinical trials [redacted].

The NNP system allows for multiple devices and modules to receive power and communicate over a FESCAN (Functional Electrical Stimulation Controller Area Network) network. The wearable system proposed here does not contain any stimulation modules; and importantly, will be worn externally at this stage. Microcontrollers in each module communicate over FESCAN using a standard Controller Area Network communication protocol. The FESCAN hardware layer utilizes a two conductor network bus that delivers power with charge balanced waveforms and enables network communication via variable pulse widths. The HIVE recording module will receive power from and send processed EMG to a rechargeable power module. The power module contains a wireless MedRadio transceiver to send signals to the socket electronics (Fig. 3). Details of the SmartLink Controller are described later in the document.

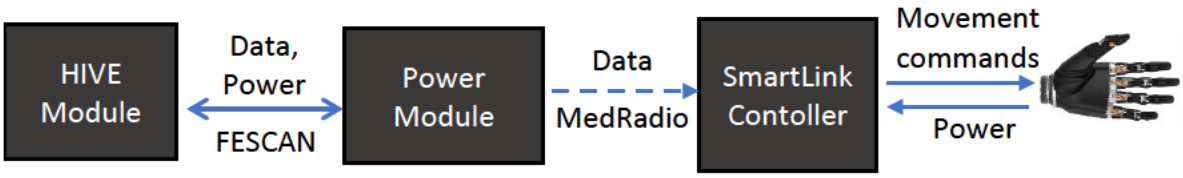

Figure 3: Functional block diagram of communication and power between system components. Dashed arrows indicate wireless communication.

The NNP power module contains rechargeable Li-Ion batteries that supply power to the entire COSMIIC system, along with the required recharging link and circuitry. Three identical 3.6V Li-ion rechargeable cells (QL0200I-A, Quallion LLC) are connected in parallel for 600mAh total capacity. Each battery cell has an external voltage protector (BQ27200DRKR, Texas Instruments) and 6v, 500mA resettable fuse (1206L050YR, Littelfuse Inc.). The power module also contains a wireless MedRadio link for communication to other devices and system programming. The power module uses a 32-bit LPC2129 microcontroller (NXP Semiconductor). Although the power module primarily functions as a power source in most applications, the processor's capabilities enable signal processing and data transfer for this application. When used with the wearable system, the power module will be recharged in between experiment sessions. The power module can be completely recharged via inductive coupling in less than 16 hours. Between uses, the power module can be placed into and taken out of a low-power 'sleep' mode by the user. It also contains a magnetically activated switch for emergency shut-down of the HIVE recording module.

Electrode leads

To record EMG signals from residual muscle and RPNIs, the wearable system will use the same [redacted] electrodes currently used in our safety and efficacy clinical trial study for upper-extremity amputation [redacted].

[redacted]

[redacted]

Risks associated with implantation of the [redacted] electrode leads:

(1) Foreign body granuloma

Granulomas may form around the implanted electrodes or electrode fragments, but are likely to be uncommon and unlikely to cause further, more serious complications[8].

Resolution: If noted, granulomas may be treated using standard protocols at the University of Michigan Health System including excision of the granuloma or extraction of the electrode or fragment if necessary.

(2) Electrode breakage

Electrodes may break if subjected to excessive strain across joints or during electrode extraction.

Mitigation: The design of the electrodes is intended to mitigate these risks. The helically-coiled leads will be flexible to handle normal strain and will be looped at each joint to further reduce strain.

Resolution: If no associated adverse reaction (infection, granuloma, etc.) is experienced, broken electrodes will be left implanted until the scheduled end of the study period to reduce the number of required extraction procedures. Adverse reactions will be treated as described and the electrode may be extracted.

(3) Pain

Electrodes may cause pain when implanted in the RPNI grafts, due to the proximity of the electrode to the peripheral nerve. The patient may also experience pain or irritation at the percutaneous site.

Mitigation: The small diameter of the electrode lead is intended to minimize discomfort at the skin and avoid irritation of the peripheral nerve. Additionally, the electrode will be sutured to tissue in such a way as to minimize movement of the electrode within the RPNI graft, further avoiding nerve irritation.

Resolution: Pain and irritation will be treated with standard pain medication. If pain control is not achieved, electrodes will be removed.

(4) Adverse reaction to materials used in the electrodes and/or connector
Rarely, participants may have some adverse reaction to the materials used in the device (e.g. allergy).

Mitigation: The materials used in the electrode lead and connector are known to be biocompatible and non-irritating.

Resolution: If an adverse response to the electrodes or connector occurs, electrodes will be removed.

Smart Link Controller

The Smart Link Controller (SLC) is designed to receive EMG signals from a wireless MedRadio (MICS) link, process the signals to predict the user's intention, and send commands to control a myoelectric prosthetic hand (see *Prosthetic Hands* section). Figure 5 shows the 3 main components of the SLC: a MICS receiver (CC1101, Texas Instruments), Microprocessor (MCU, SAME51J20A, Atmel), and Controller Area Network (SN65HVD233HD, Texas Instruments) transceiver. All components will be soldered on a Printed Circuit Board Assembly (PCBA) and the device will be enclosed in a water-resistant housing within the prosthetic.

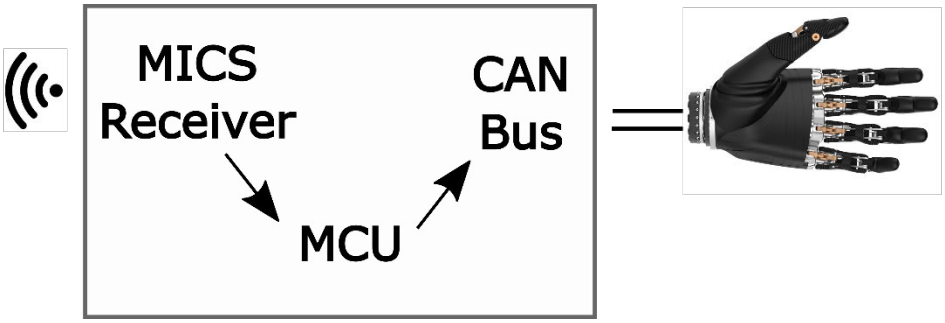

Figure 5: Block diagram of main Smart Link Controller components

The materials used in the SLC are typical for modern PCBAs. The circuit board is a flat laminated composite with internal copper circuitry. The components mounted on the circuit board are general use integrated circuits (ICs) being used as intended by the manufacturer. ICs are attached to the board with a lead-free solder with industry standard surface-mount technology (IPC Class 2).

The SLC will use state-of-the art algorithms to decode EMG signals into movement commands[9]. The choice of algorithm will depend on the operation mode of the prosthetic hand. A classifier may be used to decode grasps for intuitive grip selection, with additional

gains for proportional control[10]. Alternatively, a regressor may be used to simultaneously and independently control individual fingers[11].

The device will have minimal interactions during use. Trained study personnel will be able to connect the SLC to a laptop to record processed EMG from the neural sensing unit. Recorded EMG will be used to measure the signal strength from each electrode pair and calculate decoding parameters. A configuration mode will load new parameters onto the SLC. A test mode will be available to verify SLC function independent of the NNP. In test mode, the laptop will transfer pre-recorded EMG packets to the SLC, which will respond with decoded movement commands. Otherwise, the device operation is fixed: taking in signals, decoding intended movements, and sending outputs to the prosthesis.

The power for the SLC is supplied by the battery of the prosthesis (see section *Prosthetic Hand*). Upon startup, the SLC automatically connects to the hand and waits to receive signals from the ISU. When the SLC does not receive signals from the implant, it will stop sending predictions of movement to the prosthetic hand. This will prevent unintended or unpredictable movement of the prosthesis.

Risks associated with the SLC:

1. Stops receiving signals

   Connection with the NNP power module could be lost for many reasons, including electrical interference or the system running out of batteries. Transmission issues can interrupt the flow of data from the sensing devices to the SLC. The hand will process the last movement command it receives regardless of user intent. Potential harm to the patient is minimized with supervision.

   Mitigation: The SLC receiver will be positioned on the patient's arm to ensure reliable transmission. The CC1101 MICS receiver also has a built-in communication protocol for message verification and each header and data block has a CRC checksum to verify data integrity.

   Resolution: If the signal strength is too low to properly receive data, the SLC will activate a LED to alert the user and study personnel. The MCU will then send a no-movement command that stops the fingers from opening or closing, preventing unintended movements. If the connection cannot be resumed and no packets are received within 10 seconds, the hand will automatically open to release any object.

2. Short circuit or board damage

   Uncommon defects in manufacturing, stray conductive particles, or liquid could cause a short circuit on the PCBA. The SLC may overheat in the event of a short circuit and damage electrical components.

Mitigation: The board will be manufactured and tested by a commercial PCBA company where flying probe testing will be performed. It will be housed in a water-resistant enclosure within the socket to protect from impact or environmental contaminants. A short circuit will create an overdraw condition that will trip the power supply on the prosthetic hand (see *Prosthetic Hand* section below). This will prevent further damage.

Resolution: If the SLC is damaged or malfunctions during use, doff the prostheses and disassemble the SLC to check board for damage. After reassembly, bench test the SLC before reassembling the socket and resuming use.

3. Loss of battery power or hand communication

   Battery power could be suddenly lost if the SLC connector is loosened or becomes unplugged during use. The board will stop controlling the prosthetic hand when power or communication lines are lost, and the hand will continue to execute the last movement command.

   Mitigation: The SLC uses a connector (501330-0400, Molex) with a locking clasp. The SLC is also placed inside the socket which further minimizes the risk of an accidental disconnect.

   Resolution: Study personnel can still interact with the hand using Össur's Biosim app. Doff prostheses and inspect connections between the SLC and hand.

Prosthetic Socket

The socket fabrication method remains unchanged from the standard of care for patients requiring prosthetic restoration in the United States. A transparent plastic (Eastar™ Copolyester 6763) test socket is fabricated as the interface material between the patient's residual limb and the prosthetic device. This is same material used to fabricate prototype sockets for the clinical trial [redacted]. A prosthetist with current certification from the American Board for Certification in Prosthetics and Orthotics obtains a model of the patient's residual limb using either direct mold process with plaster or obtains the impression via 3-D scanning process to create a positive model of the residual limb, both of which are standard of care. The positive model is used to create the thermoplastic socket for the residual limb using standard clinical prosthetic protocols for anatomical suspension design. An Össur i-Limb Quantum™ prosthetic hand is connected to the socket using Ottobock™ prosthetic components including Quick Disconnect Wrist #10S1, Coupling #10S4 and Co-axial plug #9E169. Alternatively, the i-Limb hand may be used in conjunction with an i-Limb wrist rotator. The wrist rotator is attached to the outer shell of the socket with epoxy resin. The decision to use the wrist rotator will be made on an individual patient basis in consultation with a prosthetist.

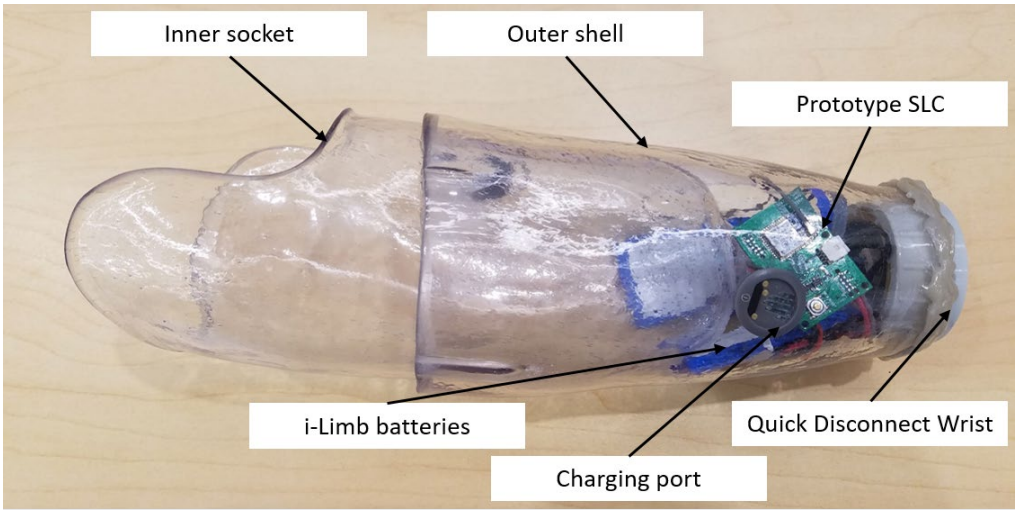

Figure 6: Example socket with electronics. Shown with prototype version of the SLC.

Risks Associated with the socket interface:

(1) Possibility of socket breaking

Mitigation: The socket will only be used within the laboratory setting with subjects who are currently upper extremity prosthetic users.

Resolution: If a socket breaks, the socket will be removed and replaced following standard of care for prosthetic users.

(2) Patient's residual limb changing volume and causing socket fit to be sub-optimal causing pain and/or tightness

Mitigation: Subject will be weighed, and residual limb girth measurements will be taken at two-week intervals.

Resolution: If the socket does become tight on the patient, silicone lubricant is used on the skin through the holes in the socket to help remove the socket. The socket will be reassessed by a certified prosthetist who will determine if a new socket will be needed.

(3) Skin irritation due to contact with socket interface

Mitigation: Socket interface material will be cleaned with alcohol prior to donning at every session. This socket material is not known to have any allergens.

Resolution: If skin irritation occurs, testing will cease until the cause of irritation is determined and resolved.

(4) Subject's skin contacting any electronic parts

Mitigation: At no time will the subject's skin have contact with the electronic parts of the socket. The electronic parts are housed in a void within the prosthesis that does not contact the subject's skin.

Resolution: If the skin gets into contact with electronic parts, the session will be stopped, and the socket will be removed. The socket will be evaluated and fixed to prevent skin contact with electronic parts.

Prosthetic hand

The terminal device will be Össur i-Limb hands and wrist rotators. The i-Limb is a Class I medical device and is 510(k) exempt. We currently have approval to use the Össur I-Limbs in our clinical trial [redacted]. We will utilize the independent motors to actuate the multiple degree of freedom finger movements. [redacted] The SLC receiver will connect to the prostheses shown in Figure 7.

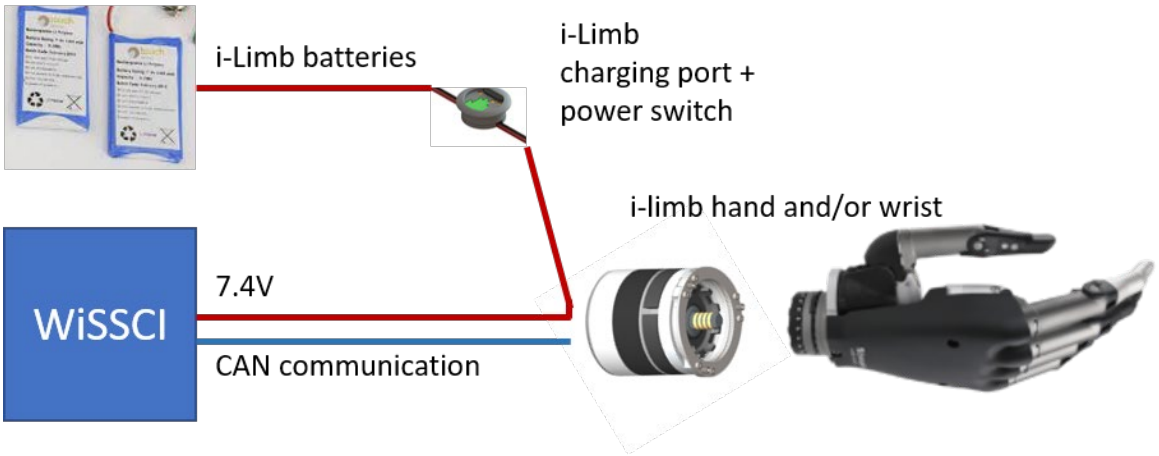

Figure 7: Power and communication connections between SLC and i-Limb

As described above, for some patients we will opt to use the wrist rotator, for others we may only use the hand. The electrical connections between our controller and the i-Limb components are the same if we are connecting to the wrist or only using a hand. The smart socket communicates with the i-Limb components over a CAN network. An application programming interface (API) is provided by Össur to control the hand and wrist. The prosthetic hand is powered by a 1300 or 2000mAh Lithium-Polymer rechargeable battery (part numbers 553559 or 704374) that are designed for and procured with the prosthetic hand. No modifications are made to the batteries or charging system. The battery size will be determined based on the size of the patient's hand, use of wrist rotator, and space available in the socket. [redacted] In the unlikely event that the combined load of the SLC and i-Limb is too high, the system is safely tripped and can be reset by connecting a charger to the charging port.

This system will only be used in supervised settings where we will adhere to Össur's usage guidelines (Attachment 2). Notably hands will:

- Only be used with an approved Össur cover
- Avoid exposure to excessive moisture, liquid, dust, vibration or shock
- Avoid operating machinery with moving parts or performing activities that may cause personal injury or damage to the hand
- Only receive maintenance or repairs from a qualified technician when the prosthesis is doffed

Per Össur's protocol: if the batteries become visibly ballooned or swelled, they will be disconnected immediately, moved to a safe area for 15 minutes, then disposed of according to local regulations. New replacement batteries will be used.

Risks associated with the prosthetic hand

(1) An overload condition can damage the prosthetic hand, for example if the hand motors draw too much current. An overload could also be caused by a short circuit which generates heat that may not dissipate in the enclosed socket.

Mitigation: The i-Limb battery and hand electronics are not modified. The i-Limb system is designed to safely trip and shut off [redacted]

Resolution: In an event of an unexpected shutdown, researchers will doff the prosthesis from the subject. We will inspect the components of the prosthesis for damage. [redacted]
After components have been inspected, replaced or repaired as necessary, the patient's system can be restarted with the following procedure: connect and disconnect the charger from the charging port, then power on.

(2) Prostheses runs out of batteries. If the patient is holding an object when this occurs, the object cannot be released.

Mitigation: Potential harm to the patient is minimized with adherence to usage guidelines (Attachment 2). Researchers will charge system regularly. During use, the Össur charging port indicates battery life in 20% increments. When the battery level reaches 5%, a red low battery warning lights up informing the patient and study personnel that the hand will power off in 3 minutes.

Resolution: Doff prostheses and recharge.

(3) Hand breaks during use.

Mitigation: Potential harm to the patient is minimized with supervision and adherence to usage guidelines. Usage guidelines are summarized above and detailed in Attachment 2.

Resolution: The prosthesis will be doffed and repaired by a specialized technician.

(4) Battery hazards associated with Lithium-Polymer batteries such as fire or leaks may pose harm to patients and study personnel.

Mitigation i-Limb batteries are unmodified and retain existing charging circuitry. [redacted] Study personnel will monitor batteries for leaks, swelling, or other signs of degradation.

Resolution Batteries will be replaced with new units as necessary.

D. PROPOSED INTENDED USE/INDICATIONS FOR USE

Identification of Condition: The goal of the study aims to treat people who have suffered upper extremity limb loss. The specific inclusion/exclusion criteria for participation in this study is given [redacted]. Briefly, this includes people with an upper limb amputation that includes the whole hand, who are in good health and are classified as American Society of Anesthesiologists (ASA) Class I or II.

Intended Use: The wireless wearable system to regenerative peripheral nerve interfaces is intended for use in upper-limb amputation patients who have received the regenerative peripheral nerve interface surgical procedure, in order to enable the use of advanced prosthetic arms and hands.

Frequency of use: The wearable system is expected to be used up to 4 hours at a time in supervised settings. The wearable system will be recharged in between uses.

Device Interaction: Please refer to Figure 1 to see a schematic of the device placement and interactions.

HIVE Wearable system

The HIVE recording module will be connected to the percutaneous bipolar electrode leads and mounted on the patients arm. A wearable power module from the Networked Neuroprosthesis (NNP) will supply power to recording module and wirelessly communicate with the SLC. The HIVE wearable system will only be used in supervised lab settings and the power module will be recharged in between uses.

Electrode Leads

The bipolar electrodes will be surgically inserted into RPNIs and any available residual innervated muscle for arm, hand and finger control. The leads will then be tunneled to a percutaneous exit site [redacted]. The insulated electrode leads will reside in the subcutaneous tissue.

SLC

The SLC will be mounted internally within the socket and does not directly contact the body. EMG signals from the sensing are received continuously via a wireless link from the NNP while the device is in use.

Socket and Prosthesis

The socket will have direct surface contact with skin to stabilize and interface the prosthetic hand to the participant. The i-Limb hand is connected to the socket or wrist rotator with a quick-disconnect connector. The i-Limb batteries are mounted internally in the socket. None of the electronic components of the prostheses contact the patient.

E. PREVIOUS DISCUSSIONS OR SUBMISSIONS

The COSMIIC is based on the NNP architecture which is under investigational use at Case Western Reserve University [redacted]. The bipolar electrode leads [redacted] are currently being used in our clinical trial study [redacted].

F. OVERVIEW OF PRODUCT DEVELOPMENT

The following groups will develop the components of the wireless systems. [redacted]. For the wearable system, Case Western Reserve University designed the NNP power module which is manufactured by Synapse Biomedical. University of Michigan will design the HIVE recording module, the PCB will be manufactured and assembled by selected vendors (Excello and Screaming Circuits). University of Michigan will also design and build the smart link controller. [redacted] Details of the planned nonclinical testing are below.

Planned Nonclinical Testing:

HIVE Wearable System

Testing will focus on verifying correct operation and electrical safety of the system. The testing is planned to be structured around key functional tests, either at the board level or as a system on a finished device.

The choice of tests will be driven by requirements, risk, and critical functions for this application. Please see the hazards analyses in Attachment 5.

Below is an initial list of expected testing, including:

- Bench testing of sensing PCBs and firmware performance
- Power supply verification (3.3V output throughout the system battery life)
- System functional testing, using a preconditioned system, including external basestation or smart link controller, and sensing devices. This test will exercise streaming communication and sensing to sense known data provided as inputs to the leads and streaming the processed data to the external device. During this test, the following metrics of each system will be measured and tested against stated requirements:
    - Accuracy of calculated neural features
    - Latency of system
    - Robustness of communication

Additional testing will be performed to demonstrate the risks of the HIVE recording module, which connects to the patient leads, are acceptable for wearable use:

- Leakage current of the HIVE recording module will comply with 14708-1 standards for future implantable use (more stringent than 60601-1)

Risk management and testing of the NNP power module charging system can be found in Appendices [redacted] of the referenced IDE[redacted]. Importantly, the NNP power module will be worn externally and the HIVE wearable system disconnected and recharged in between uses. No additional non-clinical testing is planned specific to the NNP power module. Systems level testing of the NNP power module with the HIVE recording module will be conducted as described above.

Electrode Leads
The [redacted] percutaneous electrodes are identical to our current clinical trial study [redacted]. No additional non-clinical testing is planned specific to the electrodes. Associated risks are summarized in the Device Description above [redacted].

Smart Link Controller
The SLC contains many design features to promote safe operation. As described in earlier sections, the SLC will be assembled at a commercial PCBA facility. The PCBA facility will electrically test the boards for isolation and continuity. Each SLC will be programmed and functionally tested at the University of Michigan. Programming the board verifies the operating voltage and function of the MCU. The SLC will then be configured and run in test mode with the hand on. A successful test demonstrates movements are being decoded as intended, which verifies programming of the MCU and CAN communication with the hand. We do not plan to conduct additional safety testing since the SLC does not contact the patient. Furthermore, it functions as a passive receiver and does not control the power or sensing modules.

Prosthetic Socket
The socket material and construction will follow the standard of care for patients requiring prosthetic restoration in the United States (see section C *Prosthetic Socket)*. No additional testing will be conducted.

Prosthetic Hand
The i-Limb is a commercially available Class I medical device and has been used under IDE [redacted].

Clinical Protocol:

This device is intended to be used with participants in the existing [redacted], without modification to the outcome measures, which relate to monitoring any pain associated with electrode implantation and tissue degeneration of the RPNIs.

A summary of the clinical protocol, with described changes, is below:

Primary Objective (unchanged):
The primary objective of the study is to ensure the safety of the RPNI muscle grafts with implanted electrodes. Specifically, the study will determine whether electrodes implanted in the RPNI grafts cause:

(1) Any increase or decrease in pain – nociceptive or neuropathic
(2) RPNI tissue degeneration
(3) Unanticipated electrode migration or extrusion through the skin
(4) Unanticipated complications during implantation into the RPNI grafts

Primary Endpoints (unchanged):
Pain will be assessed using two survey instruments, to be filled out by the participant before and after each surgical procedure performed and at a minimum of once per month while electrodes remain implanted:

(1) RAND 36-Item Short Form Health Survey (SF-36) (McHorney, 1993)
(2) Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (Bennett, 2001)
(3) Phantom Limb Questionnaire

RPNI tissue degeneration will be assessed by changes in pain scores (see above) and measurements of recorded efficacy at least once per month, following a 3 month postoperative recovery period, while electrodes remain implanted. Recording efficacy will be assessed using two signal quality measures:

(1) Peak-to-peak signal amplitude during maximum voluntary contraction
(2) Signal to noise ratio during maximum voluntary contraction

Electrode migration outside of the implanted RPNI graft or muscle will be assessed by changes in recording efficacy, as described above, and by ultrasound examination as necessary. Electrode extrusion and implantation complications will be assessed by adverse events reported by both the participant and the study physicians. At each study visit, the participant will be asked to report any issues, and will have a basic examination of the affected limb performed by study physicians and/or trained staff.

Secondary Objectives (unchanged):
The first secondary objective of the study is to assess the efficacy of the electrodes in recording electromyographic signals from the RPNI grafts. The second secondary objective of [redacted] is to assess the efficacy of the electrodes in delivering electrical stimulation to the RPNI grafts to evoke sensory percepts.

Secondary Endpoints (unchanged):
Recording efficacy will be assessed, for each implanted electrode, using two calculated signal quality measures, to be calculated at least once per month while electrodes remain implanted:

(1) Peak-to-peak signal amplitude during maximum voluntary contraction.

(2) Signal-to-noise ratio during maximum voluntary contraction

Stimulating efficacy will be assessed a single measure, to be recorded at least once per month while electrodes remain implanted:

(1) Stimulation threshold necessary to evoke sensory percept.

Inclusion Criteria (unchanged)

(1) Participants must be 22 years of age or older.
(2) Participants must have previously undergone an upper limb amputation proximal to the wrist or are scheduled to undergo an upper limb amputation proximal to the wrist.
(3) For participants without existing RPNI grafts (at the time of enrollment), the residual limb must have sufficient soft tissue quality to support performance of the RPNI operative procedures. Participants sustaining severe crushing or avulsion injuries with substantial superficial and deep scarring *may* not be appropriate candidates for inclusion in the study.
(4) Participants must be in good health and American Society of Anesthesiologists (ASA) Class I or II (low surgical risk).
(5) Participants must live within 2 hours of the University of Michigan Hospital.
(6) Participants must have reliable transportation.
(7) Participants must be able to attend at minimum 2 visits per month while electrodes remain implanted.
(8). Participants with previous amputations must be 6 months post-amputation.
(9) Participants who will receive an amputation at the same time as RPNI grafts and electrodes must be undergoing an elective amputation surgery where loss of useful function of the hand has occurred. They must be at least 6 months post-injury or failed limb salvage to participate.

Exclusion Criteria (unchanged)

(1) Participants may not be suffering from any severe pain syndrome including complex regional pain syndrome or severe phantom pain. All of these conditions would suggest pathological activity of the nerve and would exclude the participant from participation.
(2) Participants must not be suffering from any untreated mental health disorders and if they have any DSM-5 diagnoses, they must receive approval to participate from their mental health professional.
(3) Participants must not have any medical conditions that, in the opinion of the Principal Investigator, would place them at high risk for a surgical procedure including recent myocardial infarction, cerebrovascular accidents, deep venous thrombosis, pulmonary embolus, uncontrolled diabetes, or end stage renal disease.
(4) Participants must not have used tobacco for at least one month prior to enrollment in the study.
(5) Participants must agree to not use tobacco for the duration of the study.
(6) Participants cannot have sustained bilateral upper extremity amputation.
(7) Participants cannot be pregnant.

(8) Participants must not have other indwelling electronic implants like pacemakers, implantable cardioverter defibrillators, implantable neurostimulators, body worn insulin pumps, or body worn patient monitoring devices.
(9) Participants must not have severe peripheral vascular occlusive disease, venous hypertension of the extremity, or severe lymphedema of the extremity.
(10) Participants must not have an autoimmune condition which is not well controlled by medication.
(11) Participants will not be considered for enrollment in Primary Upper Limb Amputation with RPNI Grafts and Electrode Implantation if their amputation is a traumatic injury or cancer related.

G. SPECIFIC QUESTIONS

Saftey Testing and Risk Analysis:
Q1) The greatest safety risk of the HIVE recording module itself is the potential for electrical harm to the patient. We believe that this is sufficiently mitigated by testing the design for leakage current and our manufacutring plan. Does the FDA concur with this statement?

Q2) We believe the risk of damage to the HIVE recording module due to electrostatic discharge is mitigated since the amplifier contains ESD protection and is only handled in controlled environments. Does the FDA concur with this statement?

Q3) Overall, the system components are the same (electrodes, prosthetic hand) or have the same function (wearable HIVE recording module, Smart Link Controller) as devices currently used under our IDE in supervised settings. We believe the attached hazards analysis of the wearable HIVE recording module and this document sufficiently capture the risks of the existing and new devices. Are there any other risks we should think about for use in a supervised research setting?

Device Quality Assurace:
Q4) The HIVE recording module electronics will be manufactured to a rigorous standard (flying probe PCB test, IPC Class 3) from commercial vendors (Excello, Screaming Circuits). From there the devices are shipped to University of Michigan where each device will be programmed and benchtop tested with the power module before human use. We believe this sufficiently minimizes the risk of manufacturing errors. Does the FDA concur with this statement?

H. METHOD OF FEEDBACK

We request feedback in writing and in the form of a meeting with subsequent meeting notes. We believe these issues would be well addressed in a one-hour teleconference but would be happy to visit in person upon request. Meeting attendees from the University of Michigan would include:

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J MASTER FILE INDEX FOR REFERENCE FILES

N/A

K. LIST OF ATTACHMENTS

[redacted]

Attachment 2 – iLimb® Hand Instructions for Use

[redacted]

Attachment 5 – Hazards Analysis

[redacted]